APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

DISCLAIMER

The Clinical Coverage Guideline (CCG) is intended to supplement certain standard WellCare benefit plans and aid in administering benefits. Federal and state law, contract language, etc. take precedence over the CCG (e.g., Centers for Medicare and Medicaid Services [CMS] National Coverage Determinations [NCDs], Local Coverage Determinations [LCDs] or other published documents). The terms of a member’s particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc. may differ significantly from this Coverage Position. For example, a member’s benefit plan may contain specific exclusions related to the topic addressed in this CCG. Additionally, CCGs relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. Providers are responsible for the treatment and recommendations provided to the member. The application of the CCG is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any. All links are current at time of approval by the Medical Policy Committee (MPC) and are subject to change prior to the annual review date. Lines of business (LOB) are subject to change without notice; current LOBs can be found at www.wellcare.com. All guidelines can be found at this site as well but selecting the Provider tab, then “Tools” and “Clinical Guidelines”.

BACKGROUND

Adverse drug reactions (ADRs) are responsible for many debilitating side effects and are a major cause of death following drug therapy. It is now clear that a significant portion of these ADRs as well as therapeutic failures are caused by genetic polymorphism and genetically based inter-individual differences in drug absorption, disposition, excretion or metabolism.

The Centers for Medicare & Medicaid Services concluded that the available evidence does not demonstrate that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries. Therefore, CMS determined that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness is not reasonable and necessary.¹
Antidepressant and antipsychotic drugs are widely used in the United States. A 2011 report found that antidepressant use increased nearly 4 times from 1998 to 2008, and that 11% of Americans age ≥ 12 years were taking an antidepressant. Similarly, the use of antipsychotics more than doubled from 1995 to 2008. Antidepressant and antipsychotic drugs are primarily metabolized by members of the cytochrome P450 (CYP450) family of enzymes, which comprises > 50 enzymes that are responsible for the metabolism of most drugs. Pharmacogenetics (also known as pharmacogenomics) is the study of how an individual's genes affect their response to drugs. Specifically, pharmacogenetics is concerned with how certain genetic variants, which may be either constitutional (e.g., present in every cell of an individual's body) or acquired (e.g., present only in a specific tissue such as a tumor), affect the efficacy of a drug in a given individual and/or predict the likelihood that an individual will experience an adverse event due to the drug. Pharmacogenetic information is now included in > 200 drug labels, in 1 of 3 categories: (1) test required; (2) test recommended; and (3) information only. Recently, it has been recognized that variants in specific CYP450 genes—most notably, CYP2D6, CYP2C19, and CYP2C9—are associated with variable response to specific drugs. For example, variants in CYP2D6 and CYP2C19 have been associated with response to tamoxifen and clopidogrel, respectively. Typically, patients are categorized as being poor, intermediate, normal, or rapid metabolizers based on their genotype. Unfortunately, however, there are very little prospective data that show that knowledge of a patient's CYP450 genotype leads to improvements in patient outcomes. The STA2R SureGene Test is a pharmacogenetic test that assays variants in 7 genes, including CYP1A2, CYP2C19, and CYP2D6, as well as the serotonin receptor (SLC6A4) gene, the sulfotransferase 4A1 (SULT4A1) gene, CYP3A4, and CYP3A5, and uses this information to predict patient response to a large number of antidepressant and antipsychotic drug. Although there are many studies investigating the impact of variants in individual genes on response to individual drugs, there are no published studies evaluating the use of variant information for the 7 genes included in the STA2R SureGene Test to predict patient response to a wide range of antidepressant and antipsychotic drugs. Therefore, it is currently not possible to assess the impact of using this test in the care of patients being prescribed antidepressant or antipsychotic drugs.2

The cytochrome P450 2D6 (CYP2D6) is involved in the metabolism of most antidepressants. Comedication with a potent CYP2D6 inhibitor can convert patients with extensive metabolizer (EM) or ultra-rapid metabolizer (UM) genotypes into poor metabolizer (PM) phenotypes. Since comedication is frequent in depressed patients treated with antidepressants, we investigated the effect of the CYP2D6 composite phenotype on antidepressant efficacy, taking into account both the CYP2D6 genotype and comedication with CYP2D6 inhibitors. 87 Caucasian in patients with a major depressive episode were prospectively treated with flexible doses of antidepressant monotherapy as well as comedications and genotyped for the major CYP2D6 alleles (CYP2D6*3 rs35742686, *4 rs3892097, *5 del, *6 rs5030655, and *2XN). They were classified for CYP2D6 composite phenotype and assessed for antidepressant response after 4 weeks. In terms of genotypes (g), 6 subjects were UMg, 6 PMg, and 75 EMg. Ten p

A personalized treatment approach should be considered with the second-generation psychiatric drug mirtazapine because of high frequencies of side effects, including characteristic drowsiness. Plasma concentrations of mirtazapine in patients are influenced by many factors, including polymorphic cytochrome P450 enzymes contributing to its transformation to 8-hydroxymirtazapine and N-demethyImirtazapine. The aim of this study was to investigate the determinant factors for individual variations of metabolic clearance of mirtazapine using in vitro and in vivo methods. In vitro analyses using liver microsomes from individual humans in correlation assays and recombinantly expressed P450 enzymes revealed that CYP2D6 was the major contributor to mirtazapine 8-hydroxylation with high affinity, and that CYP3A5 catalyzed N-demethylation in a similar high-capacity manner to that of CYP3A4. CYP1A2 was a minor contributor to mirtazapine 8-hydroxylation. Metabolic clearance of mirtazapine determined in substrate depletion assays and mirtazapine 8-hydroxylation activities in individual liver microsomes were significantly lower in CYP2D6 intermediate metabolizers (IM) and poor metabolizers (PM) than in extensive metabolizers (EM) (p<0.05). Trough plasma concentration/dose ratios of mirtazapine from 14 patients were significantly higher in the CYP2D6 IM/PM group than in the EM group and were also higher in the CYP3A5 poor-expressors group than in the expressors group (p<0.05). Mirtazapine clearance in pooled human liver microsomes was inhibited by quinidine (a CYP2D6 inhibitor), ketoconazole (a CYP3A inhibitor), and in combination with risperidone and duloxetine, possible coadministered medicines. These results suggested that mirtazapine
metabolic clearance could be variously influenced by the CYP2D6 and CYP3A5 genotypes and coadministered
drugs in clinical patients.⁴

**POSITION STATEMENT**

**Applicable To:**
- ☑ Medicaid
- ☑ Medicare

For additional information on Warfarin response, see *Pharmacogenomic Testing for Warfarin Response: HS-130.*

**Exclusions**
The following are considered experimental / investigational due to a lack of established efficacy:

- STA²R SureGene Test.
- UGT1A1 molecular assay (a screening test for determining the proper dosage of irinotecan for persons with
colorectal cancer or other types of cancer (e.g., non-small-cell lung cancer)
- Genotyping for VKORC1 polymorphism (diagnostic tests to identify specific genetic variations that may be
linked to reduced/enhanced effect or severe side effects of drugs metabolized by the vitamin K epoxide
reductase complex subunit 1 gene including warfarin).
- Genotyping for apolipoprotein E (Apo E) for determining therapeutic response to lipid-lowering medications.
- Genotyping for methylenetetrahydrofolate reductase (MTHFR) for determining therapeutic response to
antifolate chemotherapy and for guiding antidepressant therapy.
- Measurement of thromboxane metabolites in urine (e.g., AspirinWorks) to evaluate aspirin resistance.
- Genetic testing for the rs3798220 allele.
- Laboratory testing to allow area under the curve (AUC)-targeted 5-fluorouracil dosing (e.g., Myriad
Genetics’ OnDose).
- Testing for genetic polymorphisms of dihydropyrimidine dehydrogenase and thymidylate synthase to predict
5-fluorouracil toxicity.
- IL28B polymorphism genotyping for interferon therapy for hepatitis C.
- GeneSightRx testing for the management of individuals treated with anti-depressant and/or anti-psychotic
medications.
- Platelet reactivity/function testing (VerifyNow P2Y12 Assay, Ultegra System Rapid Platelet Function Assay-
ASA) for individuals who have undergone percutaneous coronary intervention.
- Genecept Assay (Genomind).
- Methotrexate polyglutamates (Avise PG test).
- Beta adrenergic receptor genotyping.
- Millennium PGT (Millennium Laboratories).
- PersonaGene Genetic Panels (AIBioTech).

**Coverage**

**Cytochrome P450 polymorphisms**

WellCare considers one genotyping for CYP2C19 polymorphisms medically necessary for persons who have been
prescribed clopidogrel (Plavix). Repeat CYP2C19 genotyping has no proven value.

WellCare considers one genotyping for CYP2D6 polymorphisms medically necessary for persons who have been
prescribed doses of tetrabenazine (Xenazine) greater than 50 mg per day. Repeat CYP2D6 genotyping has no
proven value.

WellCare considers one genotyping for CYP2D6 polymorphisms medically necessary for persons with Gaucher
disease type 1 who are being considered for treatment with eliglustat (Cerdelga). Repeat CYP2D6 genotyping has
no proven value.
The following indications for CYP2D6 genotyping are considered experimental / investigational:

- For predicting response to beta blockers.
- For identifying individuals with Alzheimer's disease with different clinical response to donepezil (Aricept).

In addition, genotyping for other cytochrome P450 polymorphisms is considered experimental / investigational. Typically these tests are used to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system (e.g., opioid analgesic's, warfarin, tamoxifen, proton pump inhibitors, antipsychotic medications, and selective serotonin reuptake inhibitors).

**Genotyping for HLA-B*1502**

WellCare considers genotyping for HLA-B*1502 medically necessary for persons of Asian ancestry before commencing treatment with carbamazepine (Tegretol).

**HLA-B*5701 Screening**

WellCare considers HLA-B*5701 screening medically necessary for persons infected with HIV-1 before commencing treatment with abacavir (Ziagen).

**BRAF V600E Mutation Testing**

WellCare considers an FDA-approved test for BRAF V600E mutation (e.g., the cobas 4800 BRAF mutation test) medically necessary for persons who are considering vemurafenib (Zelboraf) for the treatment of unresectable or metastatic melanoma.

**Screening for CTFR Gene Mutations**

WellCare considers an FDA cleared test to detect the following mutations in the CTFR gene medically necessary for persons with cystic fibrosis who are being considered for treatment with ivacaftor (Kalydeco): G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N, and S549R.

WellCare considers and FDA cleared test to detect the F508del mutation in the CTFR gene medically necessary for persons with cystic fibrosis who are being considered for treatment with lumacaftor/ivacaftor (Orkambi).

**Screening for Anaplastic Lymphoma Kinase (ALK) Fusion Gene**

WellCare considers an FDA-approved test for the anaplastic lymphoma kinase (ALK) fusion gene (e.g., the Vysis ALK Break Apart FISH Probe Kit) medically necessary for persons who are considering crizotinib (Xalkori) or ceritinib (Zykadia) for the treatment of non-small cell lung cancer (NSCLC).

**MGMT (O(6)-methylguanine-DNA methyltransferase) Gene Methylation Assay**

WellCare considers the MGMT (O(6)-methylguanine-DNA methyltransferase) gene methylation assay medically necessary for predicting response to temozolomide (Temodar) in persons with glioblastoma.

**Screening for Mutation of BRAF Gene**

WellCare considers FDA-cleared tests (e.g., the THxID BRAF test) medically necessary for detecting mutation of the BRAF gene (V600E or V600K) in persons with unresectable or metastatic melanoma who are being considered for treatment with dabrafenib (Tafinlar), pembrolizumab (Keytruda), or trametinib (Mekinist).

**Screening for NS3 Q80K Polymorphism**

WellCare considers testing for the presence of virus with the NS3 Q80K polymorphism medically necessary for persons with hepatitis C virus (HCV) genotype 1a infection being considered for treatment with simeprevir (Olysio).

**BRCA Testing**

WellCare considers BRCA testing (e.g., BRACAnalysis CDx) medically necessary for women with ovarian cancer who have been treated with three or more prior lines of chemotherapy and are being considered for olaparib (Lynparza).
Covered CPT®* Codes

- **81210**: BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant
- **81211**: BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis: full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
- **81212**: - 185delAG, 5385insC, 6174delT variants
- **81214**: BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6lb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
- **81215**: - known familial variant
- **81216**: BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
- **81217**: - known familial variant
- **81220**: CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
- **81221**: - known familial variants
- **81222**: - duplication/deletion variants
- **81223**: - full gene sequence
- **81224**: - intron 8 poly-T analysis (eg, male infertility)
- **81228**: MGMT (0-6 methylguanin-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis
- **81370**: HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, -C, DRB1/3/4/5, and DQB1
- **81371**: - HLA-A, -B, and -DRB1 (eg, verification typing)
- **81372**: HLA Class I typing, low resolution (eg, antigen equivalents); complete (ie, HLA-A, -B, and -C)
- **81373**: - one locus (eg, HLA-A, or -C), each
- **81374**: - one antigen equivalent (eg, B*27), each
- **81445**: Targeted genomic sequence analysis panel, solid organ neoplasm, DNS analysis, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFA, PDGFRD, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
- **81450**: Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
- **81455**: Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1, PDGFA, PDGFRB, PGR, PIK3CA, PTEN, RET) interrogation for sequence variants and copy number variants or rearrangements, if performed
- **86812**: HLA typing: A, B, or C (eg, A10, B7, B27), single antigen
- **86813**: - A, B, or C, multiple antigens
- **86816**: - DR/DQ, single antigen
- **86817**: - DR/DQ, multiple antigens
- **86821**: - lymphocyte culture, mixed (MLC)
- **86822**: - lymphocyte culture, primed (PLC)
- **87902**: Hepatitis C virus

Non-Covered CPT®* Codes

- **81291**: MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis,

**Clinical Coverage Guideline**

Original Effective Date: 12/3/2015 - Revised: 12/8/2016, 10/5/2017
common variants (eg, 677T, 1298C)


81355  VKORC1 (vitamin K epoxide reductase complex, subunit 1) (warfarin metabolism), gene analysis, common variants (eg, -1639/3673)

81400 – 81408 Tier 2 Molecular Pathology Procedures

84431 Thromboxane metabolite(s), including thromboxane if performed, urine

Coding information is provided for informational purposes only. The inclusion or omission of a CPT, HCPCS, or ICD-10 code does not imply member coverage or provider reimbursement. Consult the member's benefits that are in place at time of service to determine coverage (or non-coverage) as well as applicable federal / state laws.

REFERENCES


MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

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